Reprinted from AMERICAN HEART JOURNAL, St. Louis
Vol. 60, No. 3, Pages 329-335, September, 1960 (Printed in the U. S. A.)

Five-Year Survival of Patients With Malignant Hypertension Treated With Antihypertensive Agents

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Franz Volhard and Theodor Fahr[1] are given credit for delineating the malignant from the benign forms of hypertension in their clinicopathologic study reported in 1914. The pathogenesis of malignant hypertension is that of a rapidly progressive disease with fatal termination, commonly ending in uremia.[1-9] It has been estimated that approximately 1 per cent of hypertensive patients develop the malignant phase.[2] Common features of the condition include severely elevated blood pressure, headache, visual disturbances, anorexia, loss of weight, weakness, and the signs and symptoms of cardiac and renal failure. The patients are most often seen during the third and fourth decades, whereas in older patients the benign forms of hypertension are commonly encountered.

In 1939, Keith, Wagener and Barker[10] divided hypertensive disease into four categories. Their distinguishing feature of Grade IV, or malignant, hypertensive patients was papilledema of the optic fundus. In their group of patients, 79 per cent were dead within 1 year of diagnosis. The 5-year survival rate was less than 1 per cent. In 1953, Schottstaedt and Sokolow,[3] in reporting on 104 patients, found that only 3 of 88 untreated patients lived longer than 2½ years. The untreated patients with adequate renal function (S.G. 1.020 or above and phenolsulfonphthalein greater than 50 per cent in 2 hours) on initial examination had an average survival period of 16.3 months as compared to the over-all mean survival of 8.4 months. In 1958, Kincaid-Smith, McMichael and Murphy[2] reported only 1 5-year survivor out of 105 untreated patients. In their series the mortality was 90 per cent at the end of 1 year.

The cardinal sign in establishing the diagnosis of malignant hypertension is the presence of papilledema. This finding may also be used as a prognostic

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Supported in part by Grant H-720 from the National Heart Institute, National Institutes of Health, and by a research grant from Irwin, Neisler & Company, Decatur, Ill.
Received for publication Jan. 8, 1960.
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guide, because with the regression of papilledema the survival rate improves. Keith and Wagener[11] found a 5-year survival of 40 per cent in 15 patients exhibiting spontaneous disappearance of papilledema. However, spontaneous regression is a rare occurrence.

Disappearance of papilledema also may occur with the reduction of blood pressure produced by antihypertensive therapy. Dustan, Schneckloth, Corcoran and Page[12] reported a 33 per cent 5-year survival in a selected series of 84 patients who received potent antihypertensive drugs. Perry and Schroeder[13] indicated a 4-year survival of 50 per cent in 82 treated patients. McMichael[14] found a 5-year life expectancy of 50 per cent in drug-treated patients who initially did not exhibit marked elevations of blood urea, whereas Smirk[15] reported a 56 per cent 4-year survival in malignant hypertensive patients. The present study summarizes the clinical and pathologic data on 64 drug-treated patients with malignant hypertension who came under observation and treatment at Mt. Alto Veterans Adminstration and Georgetown University Hospitals between the years 1949 and 1953, and reports on their follow-up to the end of 1958.

METHODS AND MATERIALS

The presence of papilledema not associated with obvious causes, such as cerebral hemorrhage or tumor, was a prerequisite for inclusion of patients in this series. Survival times were calculated from the initial observation of papilledema. In the present series there were 41 Caucasian and 23 Negro patients. Fifty-three were men and 11 were women. Their ages ranged between 23 and 61 years (mean 45.7, S.D. 10.3 years). On the basis of the needs of the individual patient and the choice of agents available at the time, the following drugs were used: various derivatives of rauwolfia, hydralazine, veratrum and its derivatives; blocking agents such as hexamethonium and pentolinium, and most recently chlorothiazide. Some patients also received chlorpromazine, phenobarbital, or meprobamate. The methods used for administering these drugs have been described elsewhere.[16-20]

RESULTS

Survival and Height of Blood Pressure.—Fourteen of 64 patients survived 5 years or longer (Fig. 1). Their ages at the time of entrance to the hospital averaged 42.3 (S.D. 9.4) years, with a range of 26 to 60 years. The average level of blood pressure prior to treatment in the group as a whole was 221/141 mm. Hg. In the patients who survived 5 years or longer, the average blood pressure before treatment was 218/140 mm. Hg. The average blood pressure after 5 years of therapy in these 14 patients was 147/99 mm. Hg. The mean of the pretreatment blood pressures in the 50 patients who did not survive for 5 years was 221/141 mm. Hg; and the mean of their last available blood pressures was 192/119 mm. Hg. The reduction of both systolic and diastolic blood pressure was significantly greater ($p < .01$) in the group who lived for 5 years than in the group who did not.

The survival rate of the Negro patients was not significantly different from that of the Caucasians; it was 54 per cent at 2 years and 20 per cent at 5 years, as compared to the 46 per cent for Caucasians at 2 years and 22 per cent at 5 years.

Funduscopic and Electrocardiographic Findings.—In 9 of the 14 patients who survived for 5 years the grade of retinopathy was recorded at or near the fifth year and found to be Grade II (Keith, Wagener and Barker classification[10])

or lower in each case. The results of electrocardiograms were available in 48 patients prior to treatment. All except 3 showed some degree of abnormality. Left ventricular hypertrophy was the most common finding. Two of the 3 patients with normal pretreatment electrocardiograms did not survive for 5 years.

Renal Function.—Pretherapy data on excretion of phenolsulfonphthalein were available in 37 patients. With 3 exceptions, all of these patients excreted less than 25 per cent of the dye in the 15-minute sample (Fig. 2). Two patients who exhibited excretions of phenolsulfonphthalein of 25 per cent or more were 5-year survivors. One is still alive 7½ years after diagnosis.

Levels of blood nitrogen as blood urea nitrogen or nonprotein nitrogen were available in 52 patients prior to therapy. They are plotted against survival time in Fig. 3. The values are elevated in the majority of cases. Three of the 14 patients who survived for 5 years had values above normal levels. However, the elevations in these 3 patients could be explained in part on the basis of congestive heart failure.

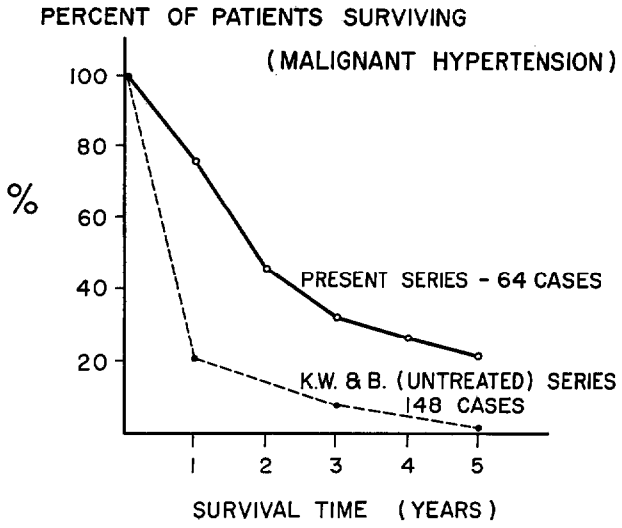

Fig. 1.—Survival times of present treated series (*solid line*) compared to the untreated series of Keith, Wagener and Barker[10] (*broken line*).

The excretion of phenolsulfonphthalein was determined prior to any treatment in 9 of the 14 patients who survived 5 years or longer. The excretion at the end of 15 minutes was 25 per cent or higher in 2 patients, 15 per cent in 4, 10 per cent in 1, 5 per cent in 1, and 2.5 per cent in 1. The blood nonprotein nitrogen was normal in all except 2 patients in whom the elevation was only moderate (44 and 58 mg. per cent, respectively) and was accompanied by clinical evidence of congestive heart failure.

Causes of Death and Autopsy Findings.—At the time of this review, 13 patients of the total of 64 were still alive. In the nonsurvivors (including 22 autopsied cases) the causes of death were diagnosed as: cerebral vascular accident in 15, cardiac complications in 12, renal in 13, pneumonia in 3, suicide in 1,

and rupture of an aneurysm of the abdominal aorta in 1. The immediate cause of death in 6 patients was not stipulated. These were cases of sudden death, and autopsy examination was not made. With the exclusion of this latter group, the most frequent fatal complications were cerebral vascular in 33 per cent, renal in 29 per cent, and cardiac in 27 per cent.

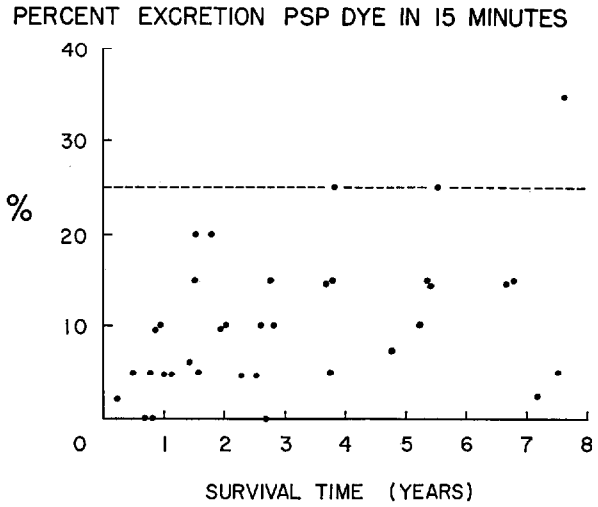

Fig. 2.—Pretreatment percentage excretions of phenolsulfonphthalein in 15-minute samples (*ordinate*) and survival times (*abscissa*). Predominance of subnormal values and lack of correlation with survival time is depicted.

In the 22 autopsied cases, 8 deaths were due primarily to renal failure, 7 to intracerebral complications, and 4 to cardiac involvement; 2 patients died of bronchopneumonia, and 1 of rupture of an abdominal aortic aneurysm. The kidneys of 5 of the 8 patients who died of uremia exhibited evidence of malignant nephrosclerosis. In the other 3, 1 showed chronic pyelonephritis, 1 chronic glomerulonephritis, and 1 severe benign nephrosclerosis. Of the 4 cardiac deaths, 2 were considered to be due to arrhythmias and 2 to myocardial infarction. In 6 patients with cerebrovascular complications the causes of death were intracranial hemorrhage (involving the pontine areas in 2 patients), whereas in 1 patient, death was thought to be due to a cerebellar pressure cone. In this patient, lumbar puncture was performed 4 days before death; during the procedure the spinal fluid pressure fell from 210 to 70 mm. of water. The blood pressure recorded on the day of the lumbar puncture was 200/138 mm. Hg. In addition to the pressure cone the autopsy disclosed an edematous brain with foci of old encephalomalacia in the cerebellum, basal ganglia, and pons, similar to the findings in cases reported previously.[21] The patient had been relatively asymptomatic under treatment with digitalis, hexamethonium, and hydralazine since a previous admission 6 months prior to the terminal event.

Atherosclerosis of the aorta and coronary and cerebral arteries was frequently observed in the 22 autopsied cases. Aortic atherosclerosis was described as being severe in 8, moderate in 9, minimal in 3, absent in 1, and was not commented

on in 1. Coronary atherosclerosis was severe in 7, moderately severe in 11, minimal in 2, absent in 1, and not described in 1. The patient who had neither aortic or coronary sclerosis was 28 years old at the time of diagnosis and died 45 months later of a pontine hemorrhage. Autopsy disclosed a relatively advanced degree of atherosclerosis in the cerebral vessels for a man of 31 years. The cerebral arteries were described in 15 cases, and moderate to marked sclerosis was seen in all 15. Included in these were 2 cases in which aneurysms of the cerebral arteries were found.

The weights of the hearts averaged 624 grams, with a range of 320 to 850 grams. The average weight of the kidneys was 133 grams (range, 70 to 200 grams). Evidence of malignant nephrosclerosis was mentioned in 13, or 59 per cent, of these patients.

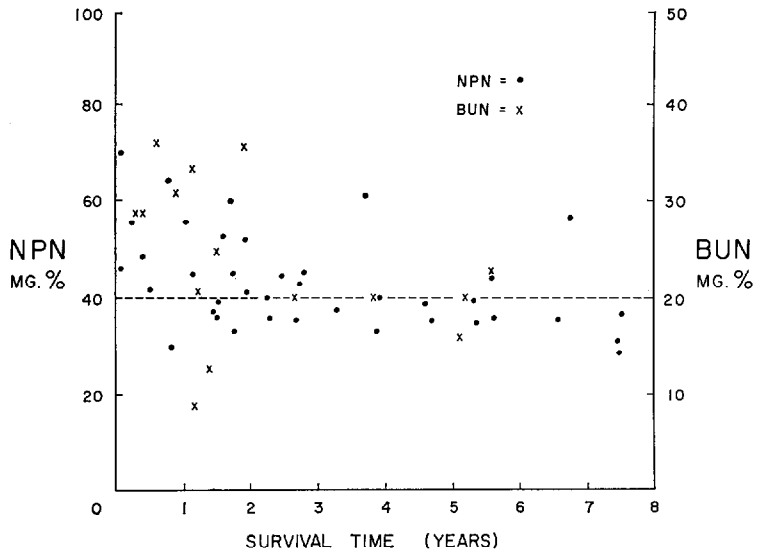

Fig. 3.—Pretreatment levels of blood urea nitrogen (*BUN*) or nonprotein nitrogen (*NPN*) (*ordinate*) compared to survival times (*abscissa*). There appears to be an approximate inverse correlation between the height of the blood urea nitrogen or nonprotein nitrogen and the survival time.

DISCUSSION

Survival time appeared to correlate significantly with the extent of renal damage prior to therapy. Thus, the majority of the patients who failed to survive for 5 years exhibited elevated values of nonprotein nitrogen. On the other hand, only 2 of the 14 patients who survived for 5 years manifested nitrogen retention, and in these 2 the uremia was moderate and associated with congestive heart failure. The survival rate was not so good in this series as that reported by others.[12-15] The reason may be that the majority of our patients had advanced renal damage at the time therapy was initiated.

Antihypertensive drug therapy seemed to change the frequency distribution of fatal complications. In the untreated series of Kincaid-Smith, McMichael and Murphy,[2] only 20 per cent died of cerebral vascular accidents, and 14 per

cent of cardiac complications; death in the remainder was due primarily to renal failure. By contrast, in the present treated series, 33 per cent of the deaths were due to cerebrovascular accidents, 27 to heart disease, and only 29 per cent to renal failure. Atherosclerosis, particularly of the cerebral vessels, also was extremely common in the treated cases. As has been pointed out by Dustan and associates,[12] premature atherosclerosis and the complications therefrom become prominent features in the patients with malignant hypertension whose lives are prolonged by antihypertensive drug treatment.

There was a significant difference in the extent of reduction of blood pressure in the patients who survived for 5 years and in those who did not; the average reduction was greater in the survivors. This result suggests that survival is related directly to the extent of reduction of blood pressure. If this is true, survival may be further improved with the development of more effective therapy. It should be pointed out, however, that, in general, the patients with less advanced vascular damage appeared to be more responsive to antihypertensive drugs. Thus, the survivors may represent the group who have not yet reached the stage of irreversible organic changes, particularly renal vascular damage. This would place a ceiling on the number of possible survivors, no matter how effective antihypertensive therapy becomes. A further reasonable assumption, on the basis of current evidence, is that a vigorous attack on the elevation of blood pressure should be made at the first sign of malignant hypertension, or better still, before the malignant phase develops.

A surprising result of this study was that the Negro patients lived almost as long as the Caucasians while under treatment. It should be pointed out, however, that there were many Negro patients with malignant hypertension who were not included in this analysis because they entered the hospital in stages of renal failure so advanced as to preclude antihypertensive therapy. Moreover, the Negro patients included in this study were the more "cooperative" patients who attended the follow-up clinic regularly and presumably were adhering to the prescribed therapeutic regimen. Although the series is small, the present results suggest that if the Negro receives and maintains adequate treatment before the stage of irreversible organic damage, he can survive as long as the Caucasian patient.

SUMMARY AND CONCLUSIONS

The case histories of 64 patients who were treated for malignant hypertension were reviewed with the purpose of determining the influence of antihypertensive drug therapy on the course of their disease. As compared to reports of survival in untreated series, the survival rate was significantly improved. The group surviving for 5 years or longer was characterized by normal or nearly normal levels of nonprotein nitrogen prior to treatment, and by significantly greater reductions of both systolic and diastolic blood pressure after treatment, as compared to the nonsurviving group. The Negro patients who received and maintained adequate treatment, and who came under observation before the advent of irreversible renal failure, survived, on the average, for as long a period as the Caucasians.

Extensive atherosclerosis, particularly of the cerebral arteries, was a consistent feature in the autopsied patients. In addition, cerebral vascular accidents and myocardial infarction were more frequent fatal complications than in untreated cases. These findings confirm the previous report of Dustan and coworkers[12] that atherosclerosis and the complications arising therefrom become prominent when the lives of these patients are prolonged by treatment.

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